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## CORRESPONDENCE



## Liberal or Restrictive Transfusion after Cardiac Surgery

**TO THE EDITOR:** In their article on red-cell transfusion, Murphy et al. (March 12 issue)<sup>1</sup> report substantial nonadherence to treatment in both study groups — one of which had a restrictive threshold for hemoglobin level in red-cell transfusions and one of which had a liberal threshold. Although nonadherence (defined as either the failure to transfuse red cells within 24 hours after a patient's hemoglobin fell below an assigned threshold or the administration of a transfusion when the hemoglobin level was above the assigned threshold) increases the likelihood of a null result for the primary outcome, it might confound the finding of increased 90-day mortality in the restrictive-threshold group, since patients in that group who received transfusions above the restrictive threshold were assumed to be sicker, whereas patients in the group with a liberal threshold were assumed to be healthier (and hence not receiving transfusions below the liberal threshold). Did the authors observe an increase in mortality in association with nonadherence to treatment in the restrictive-threshold group?

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1. Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med* 2015;372:997-1008.

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**TO THE EDITOR:** Although the Transfusion Indication Threshold Reduction (TITRe2) trial was well designed and conducted, in the absence of a difference in the composite primary outcome, the finding of a significant between-group difference in 90-day mortality is perplexing. Should this finding be real, the authors do not provide a plausible physiological explanation; humans become oxygen-supply-dependent at exceedingly low levels of oxygen delivery.<sup>1</sup> Cardiopulmonary bypass surgery has been shown to cause hemolysis with the release of free hemoglobin, which scavenges nitric oxide and leads to impaired microcirculatory flow.<sup>2,3</sup> In addition to hemolysis, the surgery causes sublethal damage to red cells that decreases their oxygen-carrying capacity and causes abnormalities in aggregation, deformability, and blood viscosity from which a patient may need months to recover.<sup>4</sup> These rheologic abnormalities may increase the patient's subsequent risk of cardiovascular events.<sup>5</sup> Is it possible that postoperative transfusion to a higher hemoglobin level may offset some of these rheologic abnor-

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malities? It is important that a confirmatory study be undertaken before a seismic change in transfusion practice occurs. Furthermore, it is important to emphasize that the findings of this study apply only to blood transfusions given after cardiopulmonary bypass surgery.

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**TO THE EDITOR:** The aim of blood transfusion is to increase the delivery of oxygen ( $\text{DO}_2$ ). In this regard, findings of the study by Murphy et al. are questionable since the study does not take into account the ratio of oxygen consumption ( $\text{VO}_2$ ) to delivery. This ratio can be determined by calculating the central venous oxygen saturation ( $\text{ScvO}_2$ ) ( $\text{ScvO}_2 = 1 - [\text{VO}_2 / \text{DO}_2]$ ), a simple calculation that can be applied in the context of cardiac surgery.<sup>1</sup> When applied in this way,  $\text{ScvO}_2$  is a determinant of individual metabolic tolerance to anemia. We have found that patients with similar hemoglobin values can be classified in two groups according to their  $\text{ScvO}_2$  values.<sup>2</sup> Whereas transfusions were beneficial in patients with low  $\text{ScvO}_2$  values, no benefits were revealed for patients with normal  $\text{ScvO}_2$  values (>70%). Like others, we have suggested that transfusion should be triggered by  $\text{ScvO}_2$  in patients with sepsis<sup>3</sup> and after major surgery.<sup>1,2</sup> Future large clinical trials

should consider the clinical usefulness of  $\text{ScvO}_2$  as an individual and physiological trigger for transfusion as compared with that of arbitrary fixed hemoglobin thresholds.

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**TO THE EDITOR:** Murphy et al. sought to compare two red-cell transfusion strategies for cardiac surgery, an important consideration given the current variability in transfusion practices<sup>1</sup> (despite recommendations by the Society of Thoracic Surgeons<sup>2</sup>). The title of the article is misleading, since their study is lacking a transfusion threshold that would be considered to be truly restrictive. There were high rates of red-cell and blood-component transfusions before randomization in both groups and very high rates of red-cell transfusion after randomization in both groups (63.7% in the restrictive-threshold group and 94.9% in the liberal-threshold group) with the mean difference in hemoglobin nadirs being only 1 g per deciliter. Despite efforts to create two different groups, the groups were similar, which makes it difficult to attach meaning to the outcomes. At best, the study compared a liberal transfusion strategy with a more liberal transfusion strategy.

Randomized clinical trials comparing restrictive and liberal transfusion practices are sorely needed. In the interim, the data from observational studies conducted by our group<sup>3</sup> and by others<sup>4</sup> strongly favor the restrictive approach and cannot be ignored.

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**TO THE EDITOR:** Murphy et al. found that a restrictive transfusion threshold after cardiac surgery did not have a significant effect on the primary composite end point (a serious infection or an ischemic event) as compared with a liberal transfusion threshold. However, all-cause mortality at 90 days was higher with the restrictive transfusion threshold. The analyses of the composite primary end point and the secondary morbidity end points did not take into account the competing risk of death and the resulting informative censoring.<sup>1-3</sup> It is possible that some patients did not acquire an infection or have an ischemic event because they died before this could happen; since mortality was significantly higher in the restrictive-transfusion group, this possibility may confound the conclusion regarding the safety of this intervention. Could the authors provide the number of patients in both groups who were alive and free of the composite end point at 90 days? Also, could the time to weaning and discharge from the intensive care unit (ICU) or hospital be determined, given that nonsurvivors would then be penalized as never having been weaned or discharged?<sup>4</sup> These additional sensitivity analyses might reveal that a restrictive transfusion threshold for this patient population is not only ineffective but also unsafe.

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**TO THE EDITOR:** Although patients requiring emergency care were excluded from the study, we wonder why no distinction was made in the subgroup analysis between patients for whom surgery was elective and patients with an acute condition (i.e., patients requiring urgent but not emergency surgery after myocardial infarction). It is well recognized that this latter group has higher rates of blood transfusion, a greater prevalence of preoperative anemia, and worse outcomes.<sup>1</sup>

There is an important distinction between patients who receive elective surgery and may remain in the ICU for 24 to 48 hours and patients who are subject to the development of complications, who require a prolonged stay in the ICU, and who are subject to the development of anemia (as occurs in >90% of patients who meet the first two criteria).<sup>2</sup> In patients with sepsis (non-cardiac), a liberal transfusion strategy confers no mortality benefit.<sup>3</sup> The pathophysiological adaptation occurring in established critical illness and the complex interplay among erythropoietin, hepcidin, and possibly neocytolysis is clearly different from the acute stress response after major surgery.<sup>4</sup> Does the transition between an elective surgical patient and a patient in need of critical care affect the point at which transfusion is triggered? We are of the opinion that timing is everything and that the important question is, when does a cardiac surgical patient become a critical care patient?

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**THE AUTHORS REPLY:** Among patients in whom there was severe nonadherence to treatment, a higher proportion in the restrictive-threshold group died as compared with the liberal-threshold group. However, this fact does not represent confounding. Although nonadherence in the restrictive-threshold group occurred among patients who were sicker than others, at randomization there would have been similar numbers of sicker patients in both groups, with those in the liberal-threshold group receiving transfusions in accordance with the protocol.

No study has shown a causal relationship between red-cell transfusion and hemolysis, the release of free hemoglobin, or impaired aggregation in patients receiving cardiac surgery. Many studies have reported the development of oxygen dependency in a high proportion of such patients in the immediate postoperative period. We agree that another large trial should be conducted to test the superiority of a liberal transfusion threshold.

We agree that there may be better indicators of the need for red-cell transfusion than hemoglobin level. In the TITRe2 trial, we compared hemoglobin thresholds because hemoglobin level is currently used to inform most decisions regarding whether or not to initiate red-cell transfusions. However, using ScvO<sub>2</sub> to guide decision making also has limitations. First, global oxygen uptake can be normal when regional hypoxia is present. Second, ScvO<sub>2</sub> does not measure oxygen utilization — the key therapeutic outcome — and there is no evidence that the use of ScvO<sub>2</sub>-guided algorithms improves this outcome. The result of the trial conducted by Rivers et al.<sup>1</sup> has not been replicated.

When planning the TITRe2 trial, we surveyed transfusion thresholds and found a range of

7.5 to 9.0 g per deciliter. No hospital used a more restrictive threshold. We expected a between-group difference in hemoglobin level of approximately 1 g per deciliter; a difference of 1.5 g per deciliter could never have been achieved even with perfect adherence, because 100% of participants in the liberal-threshold group must have breached the level of 9.0 g per deciliter, but only 33% of participants in the restrictive-threshold group were expected to breach 7.5 g per deciliter.

The numbers of patients alive and free from the composite outcome at 3 months were 599 (63.5%) in the restrictive-threshold group and 638 (66.3%) in the liberal-threshold group. Sensitivity analyses of time-to-event outcomes, in which data on deceased patients were censored at the longest period of observed time, produced hazard ratios for discharge from the ICU of 0.94 (95% confidence interval [CI], 0.86 to 1.03; *P*=0.20) and discharge from the hospital of 0.98 (95% CI, 0.90 to 1.07; *P*=0.71), findings that are consistent with those shown in Table 3 of our article. Analysis of the primary outcome as time-to-event (Fig. S3 in the Supplementary Appendix of the article, available at NEJM.org) produced a hazard ratio of 1.07 (95% CI, 0.92 to 1.25; *P*=0.37) after accounting for the competing risk of death.

Finally, in our study, more than 80% of patients underwent randomization within 24 hours of leaving the operating theater. The odds ratio for the primary outcome was similar for elective and urgent cases (post hoc test for interaction, *P*=0.23).

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Since publication of their article, the authors report no further potential conflict of interest.

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